**Circadian Sleep Disorders Network
COMMENTS on the 2015 AASM
*Draft Clinical Practice Guideline for the Treatment of Intrinsic Circadian Rhythm Sleep-Wake Disorders***

We appreciate the rigor applied to the existing studies of interventions on actual CRSWD patients. The AASM document illustrates the critical need for more and better research.

But we question the choice of metrics used to evaluate success in treating DSWPD: TST, ISL, SOT, SOffT, and DLMO. DLMO is fundamental, of course. The other metrics would all likely show improvement simply from taking hypnotics, despite the belief that hypnotics do not shift circadian timing and would not be effective long-term treatment for these disorders.

From the patient point of view, these metrics are secondary. What really matters is daytime alertness, performance on cognitive tests, subjective tiredness. These should have their own metrics. But in their absence, sleep quality metrics, such as time in deep sleep and time in REM sleep, would likely be at least as important as duration and onset/offset times. Please acknowledge this.

For evaluating treatment of N24SWD, entrainment (Yes/No) makes sense. But given the similarities with DSWPD, it is again important to evaluate daytime metrics (alertness, cognitive performance, subjective tiredness). Forcing entrainment, if it results in poor daytime performance, is not a sufficient criterion.

Most current treatments are based on phase response curves developed for normal sleepers. Even studies on interventions for shift workers are based on data on shift workers who would likely be normal sleepers when on a daytime schedule. In other words, they wouldn't have the same physiological impairments that cause CRSWDs. It should not be surprising that results of interventions are very different -- and their effectiveness less clear -- on CRSWD patients.

We suspect that there may be different physiological causes for CRSWDs in different patients. These probably include lack of sensitivity to light, over-sensitivity to light, deficiencies in the ipRGC cells of the retina, lack of melatonin production, long elimination time of melatonin, long intrinsic circadian period, differences in timing of sleep relative to internal circadian rhythms, differences in tolerance to phase mismatch, etc. [1] Which treatment is effective probably depends on the underlying cause. So investigation of a particular treatment, applied to patients satisfying (for example) the criteria for DSWPD, might be expected to succeed for patients with certain underlying causes, yet fail for those with different underlying causes. This would result in the large scatter of results observed, and hence the devaluing of these results according to the GRADES methodology. This issue is briefly alluded to in the conclusion (line 1998), but it is important and needs to be clarified and expanded.

It has been suggested that light therapy in the morning plus light avoidance in the evening may be more effective and in more patients than either therapy alone. This possibility should be singled out as meriting further research.

In the section on *Harms and Adverse Effects*, we note that there is no subsection on *Prescribed Sleep-Wake Scheduling*. It has been reported [2] that "Chronotherapy", as described for example in your Ref 94 (Czeisler et al, 1981) -- progressively delaying sleep time and wake time until reaching the desired schedule and then stabilizing -- may lead to N24SWD. Many practitioners seem unaware of this potential harm, and we feel it should be mentioned here.

A lack of sighted N24SWD subjects may be a problem for researchers. One study [3] showed that DSWPD preceded N24SWD in one fourth of the sighted people who have N24SWD.  There are enough people with DSWPD that acceptable studies can be done.  It is likely that much that applies to DSWPD will be of great help in understanding N24SWD among sighted people, and vice versa.

This does point out a problem with evidence based medicine requiring large studies, which is particularly acute for sighted N24SWD for which the currently diagnosed cohort is limited: What are doctors and patients to do when there are no large controlled trials? Just do nothing?

We also have these specific comments (preceded by the starting line number - some comments apply to both the summary and the full text):

* *98, 578* Physiologic circadian phase markers are not defined
* *225, 1085* "for a period of 28 days". Then what? No recommendation regarding permanent use of melatonin. Would a doctor conclude from this that he should only prescribe melatonin for 28 days? (pediatric: similar)
* *271* "~1000 lux, proximity to source not specified" - clarify that lux is a measurement at the patient's eye, not a characteristic of the source, and therefore shouldn't need a proximity measurement (also occurs in numerous other places)
* *977* "and experience concomitant difficulties arising at the required times." Difficulty arising is not only due to falling asleep late ("concomitant difficulties"), but also due to arising when one's internal rhythm says one should still be asleep. Natural wake time is tied to the core body temperature nadir, melatonin offset, rise in cortisol levels and other circadian cycles. Arising too early in relationship to these can be extremely difficult. Long-term health problems often result if one does this often.
* *1057* You only look at sleep time (TST, ISL, etc - see the various Tables in the Appendix) - melatonin may look better solely because of its soporific effects, not because of its chronobiotic effects.

On a related note, many of our members report that even their sleep specialists don’t know of, and sometimes deny the existence of, our disorders. We think that these AASM Guidelines would benefit from a section regarding *Problems of Access to Care*. AASM has unique influence and opportunities to ameliorate such problems for patients.

One specific example we've heard from several sighted patients with N24SWD is that their sleep specialist has insisted this can only occur in blind people. We would like to see sighted N24SWD mentioned more often, for example by saying (line 422) "non-24-hour sleep-wake rhythm disorder **in both blind and sighted patients** (N24SWD)". Even better would be to include this phrase in the title!

Some of our members report having encountered accredited sleep specialists who by default diagnose more common sleep disorders in their initial visits (e.g., sleep apnea), ignoring the patient's symptoms.  We wish to bring awareness to AASM that this barrier to CRSWD care by sleep specialists is, at times, occurring in practice.  We think that it is important for your Guideline to stress that the possibility of CRSWD should always be considered, and not simply ignored due to its assumed rarity. Even if treatment is ineffective, there are reasons patients may need a formal CRSWD diagnosis:  for school, work, jury duty, getting your kids off to school on time (parents have been taken to court because of their children’s “truancy”).

Also, many of our members report that their family physicians don’t know of, and even deny the existence of, these Circadian Rhythm Sleep-Wake Disorders. Differential diagnosis regarding CRSWDs appears to be a challenge to many non-specialized physicians. Some of our members report having been inaccurately diagnosed with a primary mental disorder, such as depression, and refused a referral to a sleep specialist. This delays accurate diagnosing and often leads to unnecessary prescribing of psychotropic medication. Coordination of care between sleep specialists and family physicians has the unique benefit in CRSWD cases to educate family physicians and help them to more easily spot such presentations in the future.

As you say in your conclusion, "This publication should serve as an impetus to address clinical research deficiencies and to promote novel inquiries for treatments of these challenging and interesting conditions." Thank you. This is sorely needed.

Sincerely,
Circadian Sleep Disorders Network

References:

1. Sack, RL et al, Circadian Rhythm Sleep Disorders: Part II, Advanced Sleep Phase Disorder, Delayed Sleep Phase Disorder, Free-Running Disorder, and Irregular Sleep-Wake Rhythm (2007) - Section 12.1, *SLEEP,* 2007; 30(11): 1484-1501 (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2082099/?tool=pubmed>)

2. Oren, DA and Wehr, TA, Hypernyctohemeral Syndrome after Chronotherapy for Delayed Sleep Phase Syndrome, *N Engl J Med* 1992; 327:1762 (<http://www.nejm.org/doi/full/10.1056/NEJM199212103272417>)

3. Hayakawa T, Uchiyama M, Kamei Y, Shibui K, Tagaya H, Asada T, Okawa M, Urata J, Takahashi K. Clinical analyses of sighted patients with non-24-hour sleep-wake syndrome: a study of 57 consecutively diagnosed cases. *SLEEP* 2005, 28(8):945-952. (Page 946, Table 1) (<http://www.ncbi.nlm.nih.gov/pubmed/16218077>)